Optimizing Dosing Based on PKPD—An overview

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This Patient Needs Antibiotics. But Which Ones, And Which Dose?

Dose Finding - The Past

Signing the amendment of Kefauver and Harris, 1962

Efficacy of the drug

Potency of a drug (MIC) Exposed to the bug In vivo (PK)
1st Question:

Does the dose matter?

Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis n=132

Treatment with fluconazole
Doses 100 – 400 mg

Individual Dose

MIC-values per individual

Determine Dose/MIC for each patient

Microbiological outcome (candida cured)

Clinical outcome

Higher dose = Lower efficacy?

Efficacy of the antimicrobial

Potency of a drug (MIC)

Exposure to the bug
in vivo (Dose; PK)

2nd Question:

Does the Dose matter in relation to the MIC (potency?)?
**MIC**

Measure of Potency – antibacterial activity

**MIC**

Lowest concentration with no visible growth after 18 hour incubation

\[ \text{MIC} = 2 \text{ mg/L} \]

**Probability of cure after treatment with fluconazole**

Oropharyngeal Candidiasis \( n=132 \)

- Prob cure correlates with Dose/MIC
- POSITIVE correlation with dose
- INVERSE correlation with MIC

Each data point represents the proportion of patients cured within a group representing a certain AUC/MIC value

Rodriguez-Tudela et al, AAC 2007

**Dose is just a means for Exposure**

**Pharmacokinetic parameters:**

Measures of Exposure

**AUC**

is usually linearly related to Dose

**Pharmacokinetic parameters:**

AUC and Peak are usually linearly related to Dose

**Does the dosing regimen matter?**

- 12.5 q6
- 25 q12
- 50 q24

Mouton et al. Drug Resist Updat. 2011 14:107-17

Mouton et al. 2007 21-44

In Antimicrobial Pharmacodynamics in Theory and Clinical Practice
randomized, double-blind phase 3 clinical trial (NCT00210964):
- comparing the efficacy of ceftobiprole with the combination CAZ and linezolid
- Ceftazidime 3dd 2 gr 2h infusion

N=390 patients included

NO clear dose response relationship

BUT...........

Muller et al, JAC 2013 68:900-906

Ceftazidime in patients with nosocomial pneumonia

randomized, double-blind phase 3 clinical trial (NCT00210964):
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- Ceftazidime 3dd 2 gr 2h infusion
- Extensive and sparse sampling of ceftazidime
- MICs of strains

N=390 patients included

N=170 with MIC
N=154 with MIC and PK-estimates
220 without Gram negatives in cultures
16 without PK estimates

Muller et al, JAC 2013 68:900-906

PK-data Culture-results with MIC-values
Individual PK parameters MIC-values per individual
Individual exposure to CAZ %fT>MIC
Microbiological outcome Clinical outcome

Exposure-response Emax model
microbiological eradication

Muller et al, JAC 2013 68:900-906

- Individual exposures to CAZ
- Categorised (%fT>MIC per 10%)
- Eradication rate per group
- 154 patients
Ceftazidime in patients with nosocomial pneumonia

CART analysis

- to differentiate between lower and higher response rate

$\%\text{f}\text{T}>\text{MIC}$ breakpoint = 44.9 %

$P<0.0001$

$\%\text{f}\text{T}>\text{MIC}$ | Success | Failure |
---|---|---|
$\geq 44.9$ | 83 (90.2%) | 9 (9.8%) |
$<44.9$ | 31 (50%) | 31 (50%) |

Muller et al, JAC 2013 68:900-906

The PKPD relationship is based on MIC AND PK exposure

- Exposure response relationship
- PK characteristics
- MIC (distribution)

How Can We Use This Information?

- Individual exposure determines outcome
- What is the individual exposure?
- Can we improve on that?
- Can we predict (how)?

BENEFIT

Target Attainment - ceftazidime

Volunteers | Mean exposure | ICU
---|---|---

Mouton et al, Clin Ther 2005 27:762

Volunteers ICU

Targets Attainment - ceftazidime

BENEFIT
**Target Attainment - ceftazidime**

- Volunteers
- ICU

**Ceftazidim in ICU patients: observed variability**

**Optimizing therapy**

- **Pharmacodynamic Target**
  - Higher MIC than expected
  - Less susceptible micro-organisms
  - Resistance
  - Lower/other EXPOSURE than expected
  - Dose / dosing regimen
  - Clearance in individual
  - Infectionsite

**Ceftazidime AGE effects 6 gr tdd**

- NP/ CIP

**At which age is it starting to be an issue?**

- CART Analysis

- Mouton & Muller Unpublished data
Ceftazidime AGE effects 6 gr tdd NP/ CIP

Multiple logistic regression
Ceftobiprole, Cure, TOC

Impact of APACHE score on microbiological eradication
Ceftobiprole, n=251

Impact of APACHE score on clinical outcome
Ceftazidime, n=104

Strategies to improve target attainment

- Probability of cure increases if %T>MIC increases
- Increase %T>MIC!
  - extended infusion
  - (continuous infusion)
Ceftazidime 8h 0.5h infusion; 2h infusion
T>MIC Increases

Comparison of outcomes of patients with APACHE II scores <17 and patients with APACHE II scores <17 (the Classification and Regression Tree [CART]-derived breakpoint) who received either an extended infusion of piperacillin-tazobactam or an intermittent infusion of piperacillin-tazobactam.

Rat survival
4 days Continuous Infusion vs Q6h

Regimen | PD50 mg/kg
--- | ---
CI | 1.82
Q6h | 24.37

Rat survival
4 days Continuous Infusion vs Q6h

Regimen | PD50 mg/kg
--- | ---
CI | 1.32
Q6h | 24.37

Kill Kinetics

- No additional killing above 4xMIC
- Killing is present / absent over short concentration range
Dose Optimization - individualized

- DETERMINE THE PK/PD TARGET
  - e.g. value of the PK/PD Index (animal studies, clinical studies)

- MICs TO BE COVERED
  - from the dosing regimen and PK, including population variability and covariates

- ESTIMATE EXPOSURE
  - from PK, including population variability and covariates

- DOSE (or choice of drug…)

Estimate exposure – How can we predict clearance in critically ill?

Creatinin Clearance In 150 Critically Ill Patients
AIDA on going clinical trial

Relation between Creatinin Clearance and Meropenem Clearance
In 238 Critically Ill Patients on 557 occasions during Continuous Infusion

Regression:
Not significant
No model assumptions

We Need Therapeutic Drug Monitoring for Antibiotics!!!!!
- In particular in patients with high/augmented clearance

- Development of fast methods to measure drug concentrations TDM!!
- For non-continuous infusion, develop and use population models
  - Analyze covariates

And the MIC part of the Equation? How to use that?
Gentamicin

Pharmacokinetic profile is very similar

PK/PD targets similar

www.eucast.org

Mouton et al, MIC-BASED DOSE ADJUSTMENT: FACTS AND FABLES. JAC 2017 in press

MICs to be covered

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Conclusions

• PK/PD explains and predicts the effects of antimicrobials
• For beta-lactams, %T>MIC is the most important predictor; for most other drugs it is fAUC/MIC
• Increasing %T>MIC to increase target attainment by adjusting the dosing regimens, TDM should be performed if no good prediction can be made
• Dosing regimens optimal for exposure may select for resistance / adjustments are clearly required
• Choose the right drug!

Mouton et al, Variation of MIC measurements: the contribution of strain and laboratory variability to measurement precision. JAC 2018, in press